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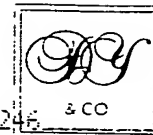
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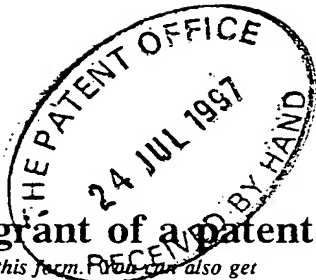
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	Patents ADP number (if you know it)	60554-2001	
	If the applicant is a corporate body, give the country/state of its incorporation	UNITED KINGDOM	
4.	Title of the invention	NOTCH	
5.	Name of your agent (if you have one)	D YOUNG & CO	
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Claims(s) 3 ✓
Abstract 1 ✓
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11. I/We request the grant of a patent on the basis of this application.

Signature

Date

D Young & Co.

24 JULY 1997

D YOUNG & CO
Agents for the Applicants

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NOTCH

The present invention relates to therapeutic compounds useful in the modification of T-cell activation. In particular it relates to compounds capable of modulating the interaction between *Notch* protein family members and their ligands and to the use of such compounds in the therapy of conditions such as graft rejection, autoimmunity, allergy, asthma and infectious diseases.

The controlled interaction between T cells and between antigen presenting cells (APC) and T cells is vital to the function of the human immune system. However in certain pathological states it may be therapeutically beneficial to modify, positively or negatively, such interactions. For example, immunosuppression is a common feature of many parasitic viral or bacterial infections. Models of "infectious tolerance" and "linked suppression" suggest that certain such organisms may induce tolerance in a small number of T cells and that these T cells then transmit this tolerance to other T cells thus preventing an effective immunological attack. In such circumstances it would therefore be desirable to inhibit the T cell interactions passing on the infectious tolerance. Alternatively in conditions such as autoimmunity, allergy and graft rejection it is desirable to induce the downregulation of an immune response by stimulation of negative T cell or T cell-APC interaction.

However until now the mechanisms underlying such T cell and T cell-APC interactions have not been understood.

WO 92/19734 purports to disclose the nucleotide sequences of the human *Notch* and *Delta* genes and amino acid sequences of their encoded proteins. The disclosure shows that the *Notch* gene family has been well characterised as essential to the correct embryological cell lineage development of insects such as Drosophila.

Proteins belonging to the *Notch* family are transmembrane receptors that contain several conserved peptide motifs. Each protein within the family displays characteristic extracellular EGF (epidermal growth factor)-like repeats and a juxtamembrane Lin-12/*Notch* motif. In addition each protein has 6-8 ankyrin repeat motifs on the cytoplasmic tail together with a PEST sequence. The *Notch* ligands have a diagnostic DSL domain (D.*Delta*, S, *Serrate*, L,*Lag2*) comprising 20-22 amino acids at the amino terminus of the protein and between 3-8 EGF-like repeats on the extracellular surface. The proteins have a short cytoplasmic tail with no conserved functional domains.

Recent evidence suggests that *Notch* signalling contributes to lineage commitment of immature T cells in the thymus, biasing thymocyte development towards the CD8+ lineage which is independent of MHC recognition (Robey E, et al. Cell 1996, in press). During maturation in the thymus, T cells acquire the ability to distinguish self antigens from those that are non-self, a process termed self tolerance (von Boehmer H, et al. Ann Rev Immunol. 1990;8:531). Mechanisms also exist in the periphery for the induction and maintenance of tolerance and in many respects their importance is under estimated. There are many experimental models of graft rejection, autoimmune disease and specific responses to allergens that clearly illustrate the ability to immunise with antigen and induce a state of specific unresponsiveness (tolerance or anergy) in the recipient. From these systems two important findings arise. Firstly, immunisation with a peptide fragment of antigen under selected conditions may inhibit specific responses not only to itself but to other regions in the same molecule provided the intact protein is used for the challenge immunisation (linked suppression; Hoyne GF, et al. J. Exp Med. 1993; 178:183. and Metzler B, Wraith DC. Int. immunol. 1993;5:1159). Secondly, as best described in experimental models of

transplantation is the phenomenon of "infectious tolerance" where it is postulated that immunocompetent cells made tolerant to a specific antigen are able to inhibit other cells from responding (Qin SX, et al. Science 1993;258:974). The immunological mechanisms underlying these phenomena have not so far been characterised.

The present invention arises from the discovery that the *Notch* receptor family and its ligands, *Delta* and *Serrate*, are expressed on the cell surface of normal adult cells of the peripheral immune system.

Hence there is provided according to the present invention, a compound capable of modulating *Notch-Notch* ligand interactions, for use in medical therapy.

The expression pattern of the *Notch* family of receptors and their ligands in the normal peripheral adult immune system has not previously been described but the present inventors have shown that T cells express mRNA *Notch 1* constitutively, while *Delta* expression is limited to only a subset of T cells in the peripheral lymphoid tissues. *Serrate* expression appears restricted to a subset of antigen presenting cells (APCs) in the periphery (Figure 1). Hence this receptor ligand family may continue to regulate cell fate decisions in tissues beyond embryonic development (Ellisen LW, et al. Cell 1991;66:649). *Notch* signalling may play a central role in the induction of peripheral unresponsiveness (tolerance or anergy) and may provide a physical explanation for linked suppression and infectious tolerance.

In a preferred embodiment of the present invention the *Notch* ligand is either *Delta* or *Serrate* or related members of these protein families.

In a further embodiment of the present invention, the compound is selected from the group comprising fusion proteins, polypeptides and peptidomimetics.

In a further preferred embodiment, the compound is a fusion protein comprising a segment of *Notch* or *Notch* ligand extracellular domain and an IgGF_c segment.

In a further preferred embodiment, the polypeptide is a derivative of a protein selected from the group comprising *Notch*, *Delta* and *Serrate* and related proteins.

A further preferred embodiment of the present invention provides the use of a compound of the present invention in the manufacture of a medicament for use in the treatment of any one or more of asthma, allergy, graft rejection, autoimmunity and infectious diseases such as those caused by *Plasmodium* species, *Microfilariae*, *Helminths*, *Mycobacteria*, *HIV*, *Cytomegalovirus*, *Pseudomonas*, *Toxoplasma*, *Echinococcus*, *Haemophilus influenza* type B, or *Toxicara*. Also provided according to the present invention are pharmaceutical formulations comprising a compound of the present invention and a pharmaceutically acceptable excipient, diluent or carrier.

The invention also provides a method for detecting immune suppression induced by an invading organism. Such organism may generate soluble forms of family members of *Serrate*, *Notch* and/or *Delta* or derivatives thereof in vivo, thus inducing infectious tolerance immunosuppression. The method comprises an assay for the presence of in vivo non-membrane bound *Serrate*, *Delta*, *Notch* or derivatives thereof and preferably comprises an antibody to *Serrate*, *Delta* or *Notch* or their derivatives.

Also provided according to the present invention are the following:-

- i. A *Notch* protein, or fragment or variant thereof, for use in therapy.
- ii. A ligand capable of binding to a *Notch* protein for use in therapy.
- iii. *Delta*, or a fragment or variant thereof, for use in therapy.
- iv. *Serrate*, or a fragment or variant thereof, for use in therapy.
- v. Use of a *Notch* protein, or fragment or variant thereof, in the manufacture of a medicament to affect natural in vivo *Notch* protein binding to a ligand.
- vi. Use of a ligand capable of binding to a *Notch* protein in the manufacture of a medicament to affect natural in vivo *Notch* protein binding to a ligand.
- vii. An assay method comprising contacting (a) *Notch* protein and a ligand capable of binding to the *Notch* protein with (b) a compound; and determining if the compound affects binding of the ligand to the *Notch* protein preferably wherein the *Notch* protein is associated with a T cell. Also, a compound when screened by this assay method.

- viii. A fusion protein comprising a *Notch* protein, or fragment or variant thereof, operably linked to at least one other protein component, preferably an immunoglobulin, or derivative or variant thereof.
- ix. A fusion protein comprising a ligand capable of binding to a *Notch* protein operably linked to at least one other protein component, preferably an immunoglobulin, or derivative or variant thereof.
- x. A *Notch* protein, or fragment or derivative thereof, for use in affecting linked suppression.
- xi. A *Notch* protein, or fragment or derivative thereof, for use in affecting infectious tolerance.
- xii. A ligand capable of binding to a *Notch* protein for use in affecting linked suppression.
- xiii. A ligand capable of binding to a *Notch* protein for use in affecting infectious tolerance.
- xiv. An assay method comprising determining the in vivo level of free *Serrate*, *Delta* or *Notch*.
- xv. A bispecific, ligand that binds to a pathogen specific antigen and to a protein which is any of: *Notch*, *Delta*, *Serrate* or

derivatives thereof, preferably purified and preferably for use in medical therapy.

Proteins or polypeptides of the present invention are preferably *Notch*, *Delta* or *Serrate* family member proteins or polypeptides or derivatives thereof. These are preferably obtained using standard techniques of recombinant technology well known to the person skilled in the art. Appropriate gene sequences for use to generate such compounds of the present invention may be obtained from publications such as WO 96/27610 and WO 92/19734. The invention is not however in any way limited by the *Notch*, *Delta* and *Serrate* sequences disclosed in these two publications. More preferably, such *Notch*, *Delta* or *Serrate* or family members, proteins or polypeptides or derivatives therefrom are fragments of the extracellular domains of *Notch*, *Delta* or *Serrate*, or family members or are derivatives of such fragments.

Pharmaceutical formulations of the present invention may be formulated according to principles well known in the art. Thus the nature of the excipient and the amount of activity will depend upon the compound of the present invention which is to be formulated.

Preferably the pharmaceutical compositions are in unit dosage form.

Dosages of compounds of the present invention, to be administered to a patient in the form of a pharmaceutical formulation, could be determined by a suitable physician.

The preferred administration route of a formulation of the present invention is any one of intravenous injection, intranasal inhalation, lung inhalation

subcutaneous, intradermal, intro-articular, intrathecally, topical, and via the alimentary tract.

The term "derivative" as used herein, in relation to proteins or polypeptides of the present invention includes any substitution of, variation of, modification of, replacement of, deletion of or addition of one (or more) amino acid residues from or to the sequence providing that the resultant protein or polypeptide possesses the capability of modulating *Notch-Notch* ligand interactions.

The term "variant" as used herein, in relation to proteins or polypeptides of the present invention includes any substitution of, variation of, modification of, replacement of, deletion of or addition of one (or more) amino acid residues from or to the sequence providing that the resultant protein or polypeptide possesses the capability of modulating *Notch-Notch* ligand interactions.

A compound may be considered to modulate *Notch-Notch* ligand interactions if it is capable of either inhibiting or enhancing the interaction of *Notch* with its ligands, preferably to an extent sufficient to provide therapeutic efficacy.

The expression "*Notch-Notch* ligand" as used herein means the interaction between a *Notch* family member and a ligand capable of binding to one or more such member.

The term therapy as used herein should be taken to encompass diagnostic and prophylactic applications.

The term "medical" includes human and veterinary applications.

As used herein, the terms protein and polypeptide may be assumed to be synonymous. Protein merely being used in a general sense to indicate a relatively longer amino acid sequence than that present in a polypeptide.

The present invention will now be described by way of non-limiting example, with reference to the accompanying drawings, in which:

Figure 1 shows the results of in situ hybridisations carried out as described in Example 1 herein;

Figure 2 shows the results of the experiment described in Example 4. Data are presented as counts per minute (cpm) ³H-Tdr incorporation 72 hours after the beginning of culture. Cpm of lymph node cells (LNC) cultured with hybridomas expressing delta ☐ or control ☐ constructs. Total numbers of cells/well = 4×10^5 (i.e the number of LNCs varies according to the ratio of hybridomas to LNC, so the cpm will vary). P110 LNC are cells primed with Der p1 (p110-131), OVA LNC are cells primed with OVA.2BB11 and 2BC3 are two different Der p1 reactive hybridomas; and

Figure 3 shows the results of the experiment described in Example 5. Data are presented as cpm of LNCs 72 hours after culture from animals immunised with control transfected ☐ or serrated transfected ☐ dendritic cells (DCs).

EXAMPLE 1

Spleen in situ hybridization

Antisense RNA probes specific for *Notch 1*, *Delta 1* and *Serrate 1* were synthesized and incorporated with digoxigenin labelled-UTP. Each probe was dissolved in hybridisation buffer, heated to 70°C for 5-10 minutes and added to TESPA coated slides containing 10mm sections of spleen or thymus that had been previously fixed with 4% paraformaldehyde + PBS. Slides were hybridized overnight at 65°C. The following day, slides were washed twice at 65°C. and twice at room temperature (RT) with 1xSSC/50% Formamide/0.1% Tween 20. Slides were washed twice with 0.1M maleic acid/0.15M NaCl/0.1% tween 20 pH 7.5 (MABT) buffer at RT and then blocked for 2 h with MABT + 20% goat serum + 296 Boehringer blocking reagent (BBR). Slides were incubated overnight at RT with anti-digoxigenin F_{ab} fragments. After four washes with MABT slides were washed a further two times in alkaline substrate buffer. The presence of bound anti-sense RNA probes was detected by incubating slides in substrate buffer containing NBT + BCIP in the dark. Slides were counterstained with haematoxylin and mounted in Depx mounting medium. The results of these hybridisations are shown in Figure 1.

EXAMPLE 2

The pIG-1 [D. Simmons, "Cloning cell surface molecules by transient surface expression in mammalian cells" pp 93-128, Cellular Interactions in Development Ed. D. Hartley, pub. Ox. Uni. Press (1993)] expression vector allows production of a fusion protein that contains the extracellular portion of Delta 1 linked to the human IgG1-F_c domain. A restriction enzyme fragment

that contained only the extracellular domain of the Delta 1 protein was cloned into the pIG-1 vector. The resultant plasmid was transformed into *E. Coli* MC 1061, and grown in SOB containing 10 μ g/ml tetracycline/ampicillin. Purified vector was used to transfect COS cells *in vitro*. COS cells were grown to 50-75% confluency and transfected with 10 μ g of plasmid DNA per dish by DEAE-dextran method. At 24 h post transfection the culture medium was replaced with culture medium containing 1% FCS and cells were cultured for a further 3-6 days *in vitro*. Cells were spun for 5mins/5000 rpm to pellet cells and debris, the supernatant was removed and stored until required. The Delta-Fc fusion was purified from culture supernatants by adding 2ml of 50% slurry of protein a Sepharose (Pharmacia) and rotated overnight at 4°C. Sepharose beads were isolated by passing culture supernatants through a 0.45 mm filter, washed and transferred to a 10 ml plastic column. The Delta-Fc fusion construct was eluted with 2 ml of elution buffer pH 4.0. The eluate was neutralised by the addition of 1M Tris base.

EXAMPLE 3

Peripheral tolerance to self antigens can be analysed in T cell receptor (TCR) transgenic mice in which the TCR ligand is expressed as a self antigen only in the periphery. Peripheral tolerance to transplantation antigens can be induced in several ways including recipient pre-treatment with T cell antibodies or blockade of costimulation. It is thereby possible to demonstrate both linked suppression and infectious tolerance. Peripheral tolerance to allergens may be induced by the intranasal delivery of allergen derived peptides. The expression of *Notch-Notch* ligands is measured on cells recruited into the airways and/or lymphoid tissues following allergen inhalation and modifications in tolerance demonstrated. Furthermore, in experimental models of infections with infectious agents, the expression of

Notch-Notch ligands can be measured on the organism (pathogen) and immunocompetent cells in the host.

EXAMPLE 4

Mice were immunised with a synthetic peptide containing an immunodominant epitope of the house dust mite allergen (HDM), Der p1 (p110-31), or with ovalbumin (OVA, hen egg white protein). One week later the lymph node cells (LNCs) were removed and cell suspensions made. Lymph nodes from animals immunised with different antigens were kept separate. These cells are referred to as primed LNCs.

T cell hybridomas were transfected with either full length Delta or a control plasmid, such that delta was expressed as a membrane protein. After two days in culture the hybridomas were irradiated to prevent them from proliferating or from producing cytokines. Therefore, the only response which was measured in the assay comes from the lymph node cells alone.

The irradiated hybridomas were added in increasing numbers to cultures containing the primed LNCs. The appropriate antigen (i.e. p110-131 or OVA) was added and the cells cultured for 24 hours. Supernatant fluids were then collected and assayed for IL-2 (a major T cell growth factor) content. Proliferative responses of the lymph node cells after 72 hours were also measured.

Lymph node cells cultured in the presence of irradiated hybridomas that expressed a control plasmid still proliferated as shown in Figure 2 and secreted IL-2 when stimulated in culture with the appropriate antigen. Their responsiveness was maintained at a ratio of 1:1 LNC:hybridoma. In contrast, the proliferative response and production of IL-2 by lymph node cells was

reduced by at least 88% when cultured in the presence of hybridomas expressing full length Delta (at a ratio of 1:1).

EXAMPLE 5

Dendritic cells (DCs) are the primary antigen presenting cell in the immune system and are critical for stimulating T cell responses. DCs were obtained from the spleen and transfected with either a plasmid expressing the full length Serrate protein or a control plasmid. The DCs were also pulsed with the HDM peptide p110-131 for 6 hours in vitro at 37 degrees. The DCs were then washed and used to immunise naive mice subcutaneously. After 7 days the draining LNCs were recovered and restimulated in culture with peptide. Since the mice were only immunised with peptide-pulsed DCs this gives us a measure of the ability of these cells to prime an immune response.

Immunisation of mice with DCs expressing Serrate resulted in a 10 fold decrease in the number of cells recovered from lymph nodes when compared to immunisation with control DCs. We further found that LNCs from mice immunised with DCs+Serrate failed to proliferate (93% reduction on control values, Figure 3) or secrete IL-2 when compared to cells from mice immunised with control DCs.

Other modifications of the present invention will be apparent to those skilled in the present art.

CLAIMS

1. A compound capable of modulating *Notch-Notch* ligand interactions, for use in medical therapy.
2. A compound according to claim 1 wherein the *Notch* ligand is either one of *Delta* and *Serrate* or derivatives thereof.
3. A compound according to either one of claims 1 and 2 which is selected from the group comprising fusion proteins, polypeptides and peptidomimetics.
4. A compound according to claim 3 wherein the fusion protein comprises a segment of *Notch-Notch* ligand extracellular domain and an IgGF_c segment.
5. A compound according to claim 3 wherein the polypeptide is a protein selected from the group comprising *Notch*, *Delta* and *Serrate* and their derivatives.
6. A compound according to any one of claims 1 to 5 wherein the medical therapy is immunotherapy.
7. A compound according to any one of claims 1 to 6 which is capable of inhibiting *Notch-Notch* ligand interactions.
8. The use of a compound according to any one of claims 1 to 6 in the manufacture of a medicament for use in the treatment of any one or

more of allergy autoimmunity, graft rejection and infectious diseases such as those caused by Plasmodium species, Microfilariae, Helminths, Mycobacteria, HIV, Cytomegalovirus, Pseudomonas, Toxoplasma, Echinococcus, Haemophilus influenza type B, or Toxicara.

9. A pharmaceutical formulation comprising a compound according to any one of claims 1 to 7 and a pharmaceutically acceptable diluent carrier or excipient.
10. A kit comprising immobilised *Notch* or family members to allow measurement of soluble *Notch* ligands originating from pathogens, transplanted grafts or cells of the host.
11. An assay method comprising contacting (a) a *Notch* protein and a ligand capable of binding to the *Notch* protein with (b) a compound; and determining if the compound affects binding of the ligand to the *Notch* protein.
12. A fusion protein comprising a *Notch* protein, or a derivative thereof, operably linked to at least one other protein component.
13. A fusion protein comprising a ligand capable of binding to a *Notch* protein operably linked to at least one other protein compound.
14. A fusion protein according to either claim 12 or claim 13 wherein the at least one other protein component is an immunoglobulin or a fragment or derivative thereof.

15. A *Notch* protein, or fragment or derivative thereof, for use in affecting linked suppression.
16. A *Notch* protein, or fragment or derivative thereof, for use in affecting infectious tolerance.
17. A ligand capable of binding to a *Notch* protein for use in affecting linked suppression.
18. A ligand capable of binding to a *Notch* protein for use in affecting infectious tolerance.
19. A ligand capable of binding to *Delta* or *Serrate* proteins or their derivatives expressed on or secreted by pathogenic organisms or transplanted grafts, for use in medical therapy.
20. An assay method comprising determining the in vivo level of soluble free *Serrate*, *Notch* or *Delta* family members or forms thereof.
21. A compound, use, formulation, kit, assay method, fusion protein, protein and ligand, substantially as described herein with reference to the accompanying Examples and Figures.

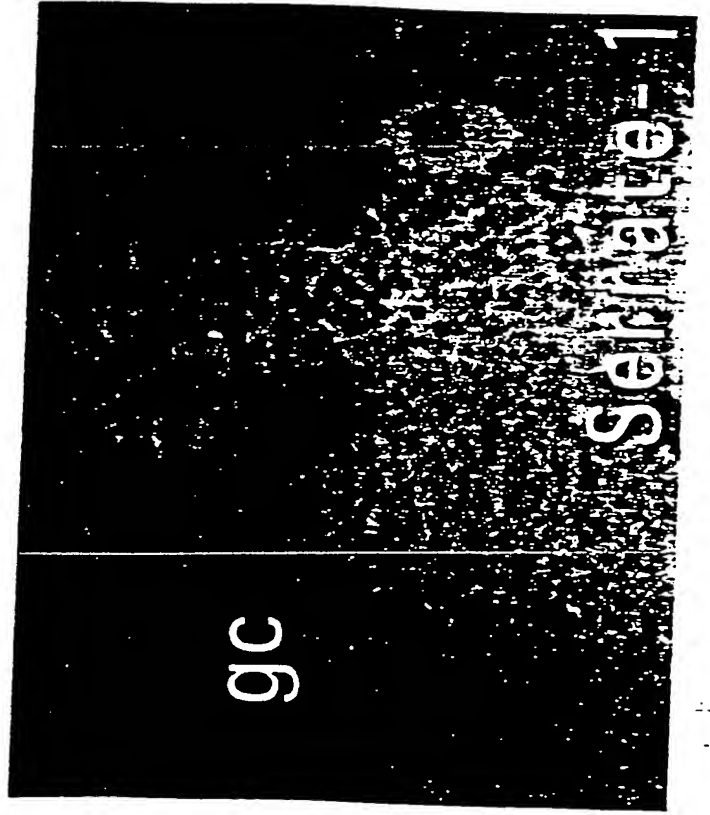
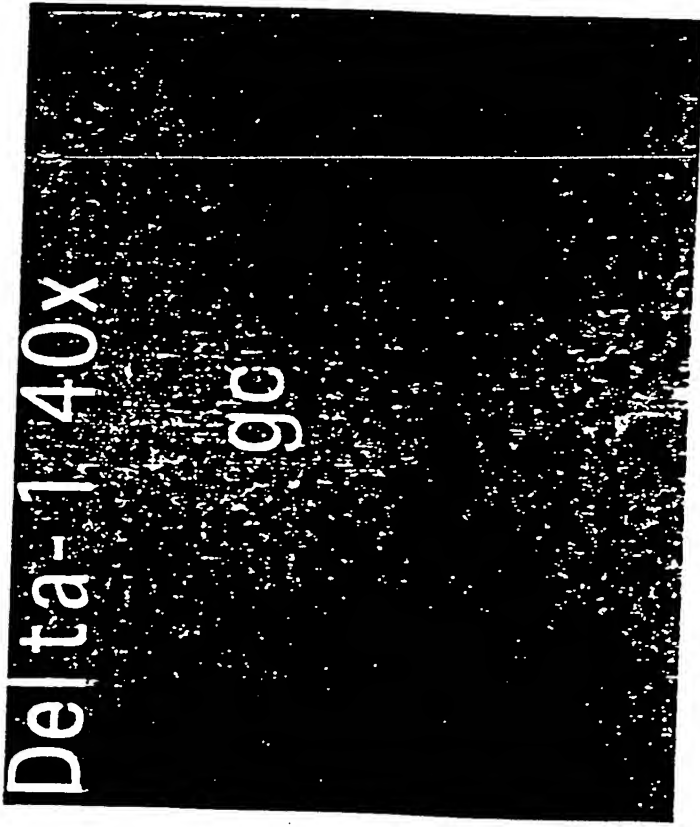
ABSTRACT

NOTCH

The present invention relates to therapeutic compounds useful in the modification of T-cell, T-cell-antigen presenting cell (APC) interactions and the interactions between pathogenic organisms and immunocompetent cells of a host. In particular it relates to compounds capable of modulating the interaction between *Notch* proteins and their ligands and to the use of such compounds in the therapy of conditions such as graft rejection, autoimmunity, allergy, and asthma and infectious diseases.

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Figure 1

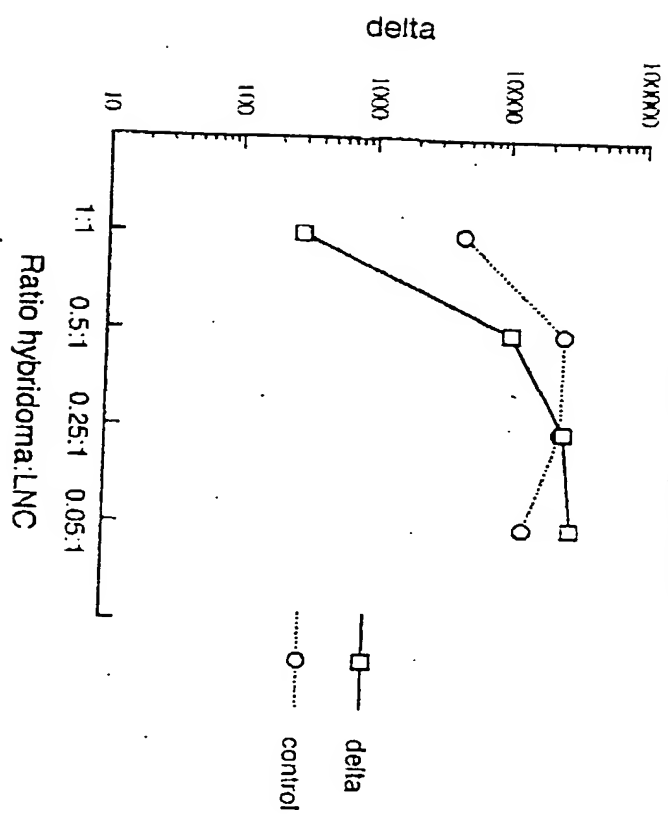


3 wk spleen
gc = germinal
centre

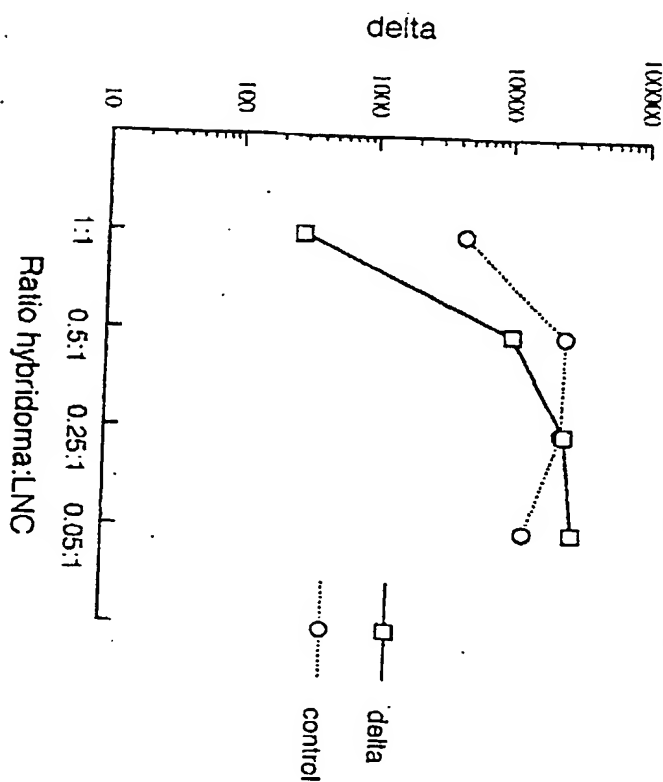
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Fig 2

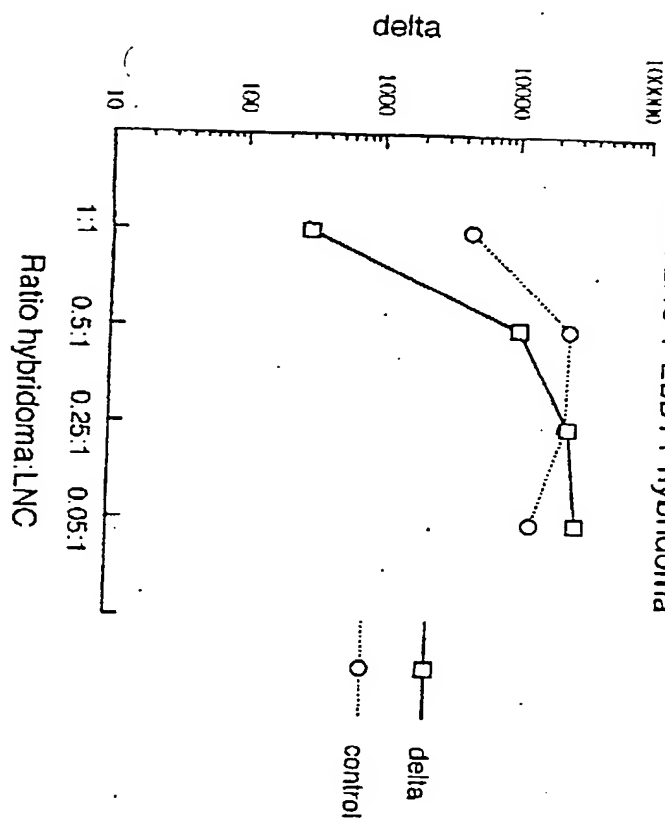
p110LNC + 2B8B11 hybridoma



p110LNC + 2BC3 hybridoma

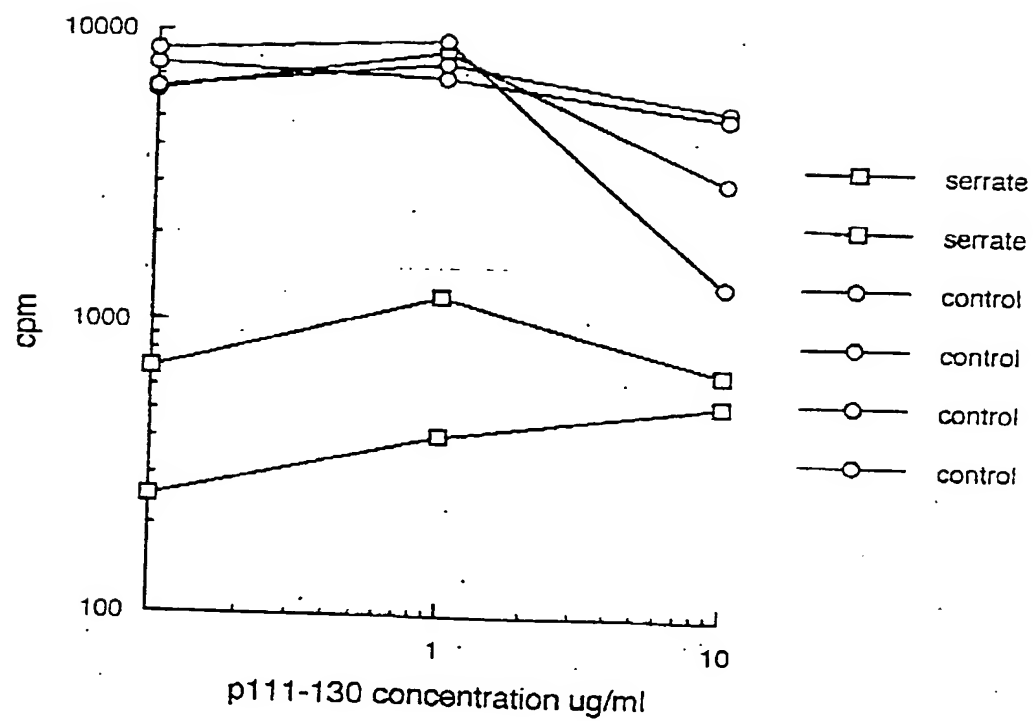


OVA LNC + 2B8B11 hybridoma



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Fig 3



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